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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53 (b))

Attorney Docket No.	LEX-0091-USA
First Inventor	C. Alexander Turner, Jr. *et al.*
Title	Novel Human Notch Ligand Proteins and Polynucleotides
Express Mail label No.	EL672756285US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231**

1. [ ] Fee Transmittal Form (e.g., PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. [X] Applicant claims small entity status. See 37 CFR 1.27.
3. [X] Specification *[Total Pages (preferred arrangement set forth below)* [26]]
   - Descriptive title of the Invention
   - Cross Reference to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the disclosure
4. [ ] Drawing(s) *(35 U.S.C.113)* *[Total Sheets* [ ]]
5. Oath or Declaration-unexecuted *[Total Pages* [2]]
   a. [ ] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1 63(d)(2) and 1 33(b).
6. [ ] Application Data Sheet See 37 CFR 1 76
7. [ ] CD-ROM or CD-R in duplicate, large table or Compute Program (*Appendix*)
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [X] paper
   c. [ ] Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. [ ] Assignment Papers (cover sheet & document(s))
10. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
11. [ ] English Translation Document *(if applicable)*
12. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
13. [ ] Preliminary Amendment
14. [X] Return Receipt Postcard (MPEP 503) (*Should be specifically itemized*)
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16. [ ] Other. ....

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[ ] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No.:_____

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NOVEL HUMAN *NOTCH* LIGAND PROTEINS AND POLYNUCLEOTIDES ENCODING THE SAME

The present application claims the benefit of U.S. Provisional Application Number 60/165,959 which was filed on November 17, 1999 and is herein incorporated by reference in its entirety.

1. INTRODUCTION

The present invention relates to the discovery, identification, and characterization of novel human polynucleotides encoding proteins that share sequence similarity with mammalian SEL-1 proteins. The invention encompasses the described polynucleotides, host cell expression systems, the encoded proteins, fusion proteins, polypeptides and peptides, antibodies to the encoded proteins and peptides, and genetically engineered animals that either lack or over express the disclosed genes, antagonists and agonists of the proteins, and other compounds that modulate the expression or activity of the proteins encoded by the disclosed genes that can be used for diagnosis, drug screening, clinical trial monitoring and the treatment of physiological disorders.

2. BACKGROUND OF THE INVENTION

SEL-1 proteins are negative regulators of *Notch* family receptors. *Notch* receptors and their associated signaling pathways have been associated with development, apoptosis, neuron growth and maintenance. Genetic alterations in *Notch* receptors and their ligands have been associated with multiple human processes and disorders such as diabetes, cancer (*inter alia* pancreatic cancer and insulinomas), stroke, Alzheimer's and other neurodegenerative diseases, cholesterol and fat metabolism (HMG CoA reductase degradation), blood pressure abnormalities, Coronary

artery disease and immunity (Donoviel and Bernstein, WO 99/27088, incorporated by reference in its entirety).

3. SUMMARY OF THE INVENTION

The present invention relates to the discovery, identification, and characterization of nucleotides that encode novel human proteins, and the corresponding amino acid sequences of these proteins. The novel human proteins (NHPs) described for the first time herein share structural similarity with animal *Notch* ligands, and particularly SEL-1. As such, the novel *Notch* ligand proteins represent new members of the *Notch* ligand family, a family that has a range of homologues and orthologs that transcend phyla and species.

The novel human nucleic acid sequences described herein, encode proteins/open reading frames (ORFs) of 689, 688, 590, 418, 499, 576, and 575 amino acids in length (see SEQ ID NOS: 2, 4, 6, 8, 10, 12, and 14 respectively).

The invention also encompasses agonists and antagonists of the described NHPs, including small molecules, large molecules, mutant NHPs, or portions thereof that compete with native NHP, peptides, and antibodies, as well as nucleotide sequences that can be used to inhibit the expression of the described NHPs (*e.g.*, antisense and ribozyme molecules, and gene or regulatory sequence replacement constructs) or to enhance the expression of the described NHP sequences (*e.g.*, expression constructs that place the described sequence under the control of a strong promoter system), and transgenic animals that express a NHP transgene, or "knock-outs" (which can be conditional) that do not express a functional NHP.

Further, the present invention also relates to processes for identifying compounds that modulate, *i.e.*, act as agonists or antagonists, of NHP expression and/or NHP activity that utilize purified preparations of the described NHPs and/or NHP product, or

cells expressing the same. Such compounds can be used as therapeutic agents for the treatment of any of a wide variety of symptoms associated with biological disorders, including, but not limited to, diabetes, heart disease and cancer.

4. DESCRIPTION OF THE SEQUENCE LISTING AND FIGURES

The Sequence Listing provides the sequences of the NHP ORFs encoding the described NHP amino acid sequences.

5. DETAILED DESCRIPTION OF THE INVENTION

The NHPs, described for the first time herein, are novel proteins that are expressed in, *inter alia,* human testis cells and gene trapped human cell lines. The present invention encompasses the nucleotides presented in the Sequence Listing, host cells expressing such nucleotides, the expression products of such nucleotides, and: (a) nucleotides that encode mammalian homologs of the described sequences, including the specifically described NHPs, and the NHP products; (b) nucleotides that encode one or more portions of the NHPs that correspond to functional domains, and the polypeptide products specified by such nucleotide sequences, including but not limited to the novel regions of any active domain(s); (c) isolated nucleotides that encode mutant versions, engineered or naturally occurring, of the described NHPs in which all or a part of at least one domain is deleted or altered, and the polypeptide products specified by such nucleotide sequences, including but not limited to soluble proteins and peptides in which all or a portion of the signal sequence in deleted; (d) nucleotides that encode chimeric fusion proteins containing all or a portion of a coding region of an NHP, or one of its domains (*e.g.*, a receptor or ligand binding domain, accessory protein/self-association domain, etc.) fused to another peptide or polypeptide; or (e) therapeutic or diagnostic derivatives of the described polynucleotides such as

oligonucleotides, antisense polynucleotides, ribozymes, dsRNA, or gene therapy constructs comprising a sequence first disclosed in the Sequence Listing. As discussed above, the present invention includes: (a) the human DNA sequences presented in the Sequence Listing (and vectors comprising the same) and additionally contemplates any nucleotide sequence encoding a contiguous NHP open reading frame (ORF) that hybridizes to a complement of a DNA sequence presented in the Sequence Listing under highly stringent conditions, *e.g.*, hybridization to filter-bound DNA in 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3) and encodes a functionally equivalent gene product. Additionally contemplated are any nucleotide sequences that hybridize to the complement of the DNA sequence that encode and express an amino acid sequence presented in the Sequence Listing under moderately stringent conditions, *e.g.*, washing in 0.2xSSC/0.1% SDS at 42°C (Ausubel et al., 1989, *supra*), yet still encode a functionally equivalent NHP product. Functional equivalents of a NHP include naturally occurring NHPs present in other species and mutant NHPs whether naturally occurring or engineered (by site directed mutagenesis, gene shuffling, directed evolution as described in, for example, U.S. Patent No. 5,837,458). The invention also includes degenerate nucleic acid variants of the disclosed NHP polynucleotide sequences.

Additionally contemplated are polynucleotides encoding NHP ORFs, or their functional equivalents, encoded by polynucleotide sequences that are about 99, 95, 90, or about 85 percent similar or identical to corresponding regions of the nucleotide sequences of the Sequence Listing (as measured by BLAST sequence comparison analysis using, for example, the GCG sequence analysis package using standard default settings).

The invention also includes nucleic acid molecules, preferably DNA molecules, that hybridize to, and are therefore the complements of, the described NHP nucleotide sequences. Such hybridization conditions may be highly stringent or less highly stringent, as described above. In instances where the nucleic acid molecules are deoxyoligonucleotides ("DNA oligos"), such molecules are generally about 16 to about 100 bases long, or about 20 to about 80, or about 34 to about 45 bases long, or any variation or combination of sizes represented therein that incorporate a contiguous region of sequence first disclosed in the Sequence Listing. Such oligonucleotides can be used in conjunction with the polymerase chain reaction (PCR) to screen libraries, isolate clones, and prepare cloning and sequencing templates, etc.

Alternatively, such NHP oligonucleotides can be used as hybridization probes for screening libraries, and assessing gene expression patterns (particularly using a micro array or high-throughput "chip" format). Additionally, a series of the described NHP oligonucleotide sequences, or the complements thereof, can be used to represent all or a portion of the described NHP sequences. The oligonucleotides, typically between about 16 to about 40 (or any whole number within the stated range) nucleotides in length may partially overlap each other and/or the NHP sequence may be represented using oligonucleotides that do not overlap. Accordingly, the described NHP polynucleotide sequences shall typically comprise at least about two or three distinct oligonucleotide sequences of at least about 18, and preferably about 25, nucleotides in length that are each first disclosed in the described Sequence Listing. Such oligonucleotide sequences may begin at any nucleotide present within a sequence in the Sequence Listing and proceed in either a sense (5'-to-3') orientation vis-a-vis the described sequence or in an antisense orientation.

For oligonucleotide probes, highly stringent conditions may refer, *e.g.*, to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligos), 48°C (for 17-base oligos), 55°C (for 20-base oligos), and 60°C (for 23-base oligos). These nucleic acid molecules may encode or act as NHP gene antisense molecules, useful, for example, in NHP gene regulation (for and/or as antisense primers in amplification reactions of NHP nucleic acid sequences). With respect to NHP gene regulation, such techniques can be used to regulate biological functions. Further, such sequences may be used as part of ribozyme and/or triple helix sequences that are also useful for NHP gene regulation.

Inhibitory antisense or double stranded oligonucleotides can additionally comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide can also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide will comprise at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or any combination or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an α-anomeric oligonucleotide. An α-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gautier *et al.*, 1987, Nucl. Acids Res. *15*:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue *et al.*, 1987, Nucl. Acids Res. *15*:6131-6148), or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, FEBS Lett. *215*:327-330). Alternatively, double stranded RNA can be used to disrupt the expression and function of a targeted NHP.

Oligonucleotides of the invention can be synthesized by standard methods known in the art, *e.g.* by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides can be synthesized by the method of Stein *et al.* (1988, Nucl. Acids Res. *16*:3209), and methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin *et al.*, 1988, Proc. Natl. Acad. Sci. U.S.A. *85*:7448-7451), etc.

Low stringency conditions are well known to those of skill in the art, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are derived. For guidance regarding such conditions see, for example, Sambrook *et al.*, 1989, Molecular Cloning, A Laboratory Manual (and periodic updates thereof), Cold Springs Harbor Press, N.Y.; and Ausubel *et al.*, 1989, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y.

Alternatively, suitably labeled NHP nucleotide probes can be used to screen a human genomic library using appropriately stringent conditions or by PCR. The identification and characterization of human genomic clones is helpful for identifying polymorphisms (including, but not limited to, nucleotide repeats, microsatellite alleles, single nucleotide polymorphisms, or coding single nucleotide polymorphisms), determining the genomic structure of a given locus/allele, and designing diagnostic tests. For example, sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), etc., that can be used in diagnostics and pharmacogenomics.

Further, a NHP sequence homolog can be isolated from nucleic acid from an organism of interest by performing PCR using two degenerate or "wobble" oligonucleotide primer pools designed on the basis of amino acid sequences within the NHP products disclosed herein. The template for the reaction may be total RNA, mRNA, and/or cDNA obtained by reverse transcription of mRNA prepared from human or non-human cell lines or tissue known or suspected to express an allele of a NHP gene.

The PCR product can be subcloned and sequenced to ensure that the amplified sequences represent the sequence of the desired NHP. The PCR fragment can then be used to isolate a full length cDNA clone by a variety of methods. For example, the amplified fragment can be labeled and used to screen a cDNA library, such as a bacteriophage cDNA library. Alternatively, the labeled fragment can be used to isolate genomic clones via the screening of a genomic library.

PCR technology can also be used to isolate full length cDNA sequences. For example, RNA can be isolated, following standard procedures, from an appropriate cellular or tissue source (*i.e.*,

one known, or suspected, to express a NHP sequence, such as, for example, testis or pancreatic tissue). A reverse transcription (RT) reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid may then be "tailed" using a standard terminal transferase reaction, the hybrid may be digested with RNase H, and second strand synthesis may then be primed with a complementary primer. Thus, cDNA sequences upstream of the amplified fragment can be isolated. For a review of cloning strategies that can be used, see *e.g.*, Sambrook *et al.*, 1989, *supra*.

A cDNA encoding a mutant NHP sequence can be isolated, for example, by using PCR. In this case, the first cDNA strand may be synthesized by hybridizing an oligo-dT oligonucleotide to mRNA isolated from tissue known or suspected to be expressed in an individual putatively carrying a mutant NHP allele, and by extending the new strand with reverse transcriptase. The second strand of the cDNA is then synthesized using an oligonucleotide that hybridizes specifically to the 5' end of the normal gene. Using these two primers, the product is then amplified via PCR, optionally cloned into a suitable vector, and subjected to DNA sequence analysis through methods well known to those of skill in the art. By comparing the DNA sequence of the mutant NHP allele to that of a corresponding normal NHP allele, the mutation(s) responsible for the loss or alteration of function of the mutant NHP gene product can be ascertained.

Alternatively, a genomic library can be constructed using DNA obtained from an individual suspected of or known to carry a mutant NHP allele (*e.g.*, a person manifesting a NHP-associated phenotype such as, for example, obesity, high blood pressure, an inflammatory disorder, etc.), or a cDNA library can be constructed using RNA from a tissue known, or suspected, to express a mutant NHP allele. A normal NHP gene, or any suitable fragment thereof,

can then be labeled and used as a probe to identify the corresponding mutant NHP allele in such libraries. Clones containing mutant NHP gene sequences can then be purified and subjected to sequence analysis according to methods well known to those skilled in the art.

Additionally, an expression library can be constructed utilizing cDNA synthesized from, for example, RNA isolated from a tissue known, or suspected, to express a mutant NHP allele in an individual suspected of or known to carry such a mutant allele. In this manner, gene products made by the putatively mutant tissue can be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against a normal NHP product, as described below. (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Press, Cold Spring Harbor.)

Additionally, screening can be accomplished by screening with labeled NHP fusion proteins, such as, for example, alkaline phosphatase-NHP or NHP-alkaline phosphatase fusion proteins. In cases where a NHP mutation results in an expressed gene product with altered function (*e.g.*, as a result of a missense or a frameshift mutation), polyclonal antibodies to a NHP are likely to cross-react with a corresponding mutant NHP gene product. Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis according to methods well known in the art.

The invention also encompasses (a) DNA vectors that contain any of the foregoing NHP coding sequences and/or their complements (*i.e.*, antisense); (b) DNA expression vectors that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences (for example, baculo virus as described in U.S. Patent No. 5,869,336 herein incorporated by reference); (c) genetically engineered host cells that contain any of the foregoing NHP coding

sequences operatively associated with a regulatory element that directs the expression of the coding sequences in the host cell; and (d) genetically engineered host cells that express an endogenous NHP gene under the control of an exogenously introduced regulatory element (*i.e.*, gene activation). As used herein, regulatory elements include, but are not limited to, inducible and non-inducible promoters, enhancers, operators and other elements known to those skilled in the art that drive and regulate expression. Such regulatory elements include but are not limited to the human cytomegalovirus (hCMV) immediate early gene, regulatable, viral elements (particularly retroviral LTR promoters), the early or late promoters of SV40 adenovirus, the *lac* system, the *trp* system, the *TAC* system, the *TRC* system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, the promoter for 3-phosphoglycerate kinase (PGK), the promoters of acid phosphatase, and the promoters of the yeast α-mating factors.

Also encompassed by the present invention are novel protein constructs engineered in such a way that they facilitate transport of the NHP to the target site, to the desired organ, across the cell membrane and/or to the nucleus where the NHP can exert its function activity. This goal may be achieved by coupling of the NHP to a cytokine or other ligand that would direct the NHP to the target organ and facilitate receptor mediated transport across the membrane into the cytosol. Conjugation of NHPs to antibody molecules or their Fab fragments could be used to target cells bearing a particular epitope. Attaching the appropriate signal sequence to the NHP would also transport the NHP to the desired location within the cell. Alternatively targeting of NHP or its nucleic acid sequence might be achieved using liposome or lipid complex based delivery systems. Such technologies are described in U.S. Patents Nos. 4,594,595, 5,459,127, 5,948,767 and 6,110,490

and their respective disclosures which are herein incorporated by reference in their entirety.

The present invention also encompasses antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists and agonists of the NHP, as well as compounds or nucleotide constructs that inhibit expression of a NHP gene (transcription factor inhibitors, antisense and ribozyme molecules, or gene or regulatory sequence replacement constructs), or promote the expression of a NHP (*e.g.*, expression constructs in which NHP coding sequences are operatively associated with expression control elements such as promoters, promoter/enhancers, etc.).

The NHPs or NHP peptides, NHP fusion proteins, NHP nucleotide sequences, antibodies, antagonists and agonists can be useful for the detection of mutant NHPs or inappropriately expressed NHPs for the diagnosis of disease. The NHP proteins or peptides, NHP fusion proteins, NHP nucleotide sequences, host cell expression systems, antibodies, antagonists, agonists and genetically engineered cells and animals can be used for screening for drugs (or high throughput screening of combinatorial libraries) effective in the treatment of the symptomatic or phenotypic manifestations of perturbing the normal function of NHP in the body. The use of engineered host cells and/or animals may offer an advantage in that such systems allow not only for the identification of compounds that bind to the endogenous receptor for an NHP, but can also identify compounds that trigger NHP-mediated activities or pathways.

Finally, the NHP products can be used as therapeutics. For example, soluble derivatives such as NHP peptides/domains corresponding the NHPs, NHP fusion protein products (especially NHP-Ig fusion proteins, *i.e.*, fusions of a NHP, or a domain of a NHP, to an IgFc), NHP antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists or agonists (including compounds that modulate or act on downstream targets in a NHP-

mediated pathway) can be used to directly treat diseases or disorders. For instance, the administration of an effective amount of soluble NHP, or a NHP-IgFc fusion protein or an anti-idiotypic antibody (or its Fab) that mimics the NHP could activate or effectively antagonize the endogenous NHP receptor. Soluble NHPs can also be modified by proteolytic cleavage to active peptide products (*e.g.*, any novel peptide sequence initiating at any one of the amino acids presented in the Sequence Listing and ending at any downstream amino acid). Such products or peptides can be further subject to modification such as the construction of NHP fusion proteins and/or can be derivatized by being combined with pharmaceutically acceptable agents such as, but not limited to, polyethylene glycol (PEG).

Nucleotide constructs encoding such NHP products can be used to genetically engineer host cells to express such products *in vivo;* these genetically engineered cells function as "bioreactors" in the body delivering a continuous supply of a NHP, a NHP peptide, or a NHP fusion protein to the body. Nucleotide constructs encoding functional NHPs, mutant NHPs, as well as antisense and ribozyme molecules can also be used in "gene therapy" approaches for the modulation of NHP expression. Thus, the invention also encompasses pharmaceutical formulations and methods for treating or preventing biological disorders such as, but not limited to, Alzheimer's Disease, diabetes, cancer, neurodegenerative diseases such as Parkinson's disease, stroke, vascular dementia, and conditions requiring modulation of fat and cholesterol metabolism such as coronary artery disease.

Various aspects of the invention are described in greater detail in the subsections below.

5.1 THE NHP SEQUENCES

The cDNA sequences and the corresponding deduced amino acid sequences of the described NHPs are presented in the Sequence Listing. The NHP nucleotides were obtained from human gene trapped sequence tags and cDNA clones from a human testis cDNA library. A coding region single nucleotide polymorphism was observed during the generation of the described NHPs which consists of an A-to-G (or vice-versa) transition at base number 1,177 of, for example, SEQ ID NO:1 which results the presence of an glu or a lys at corresponding amino acid position 393 of, for example, SEQ ID NO:2.

Because of the diverse activities that have been associated with *Notch* signaling pathways, *Notch* receptors, and their associated ligands and antagonists have been subject to intense scientific scrutiny. For examples of how the described NHPs, or related *Notch* receptors can be produced, antagonized, used, processed, applied, and delivered, see, for example, U.S. Patent Nos. 5,786,158 and 5,780,300, and 5,856,441 the disclosures of which are hereby incorporated by reference in their entirety. Given their structural relatedness to *Notch* ligands, the described NHPs are suitable for use and modification as contemplated for other *Notch* ligands and antagonists.

5.2 NHPS AND NHP POLYPEPTIDES

NHPs, polypeptides, peptide fragments, mutated, truncated, or deleted forms of the NHPs, and/or NHP fusion proteins can be prepared for a variety of uses. These uses include, but are not limited to, the generation of antibodies, as reagents in diagnostic assays, for the identification of other cellular gene products related to a NHP, as reagents in assays for screening for compounds that can be as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders and disease.

The Sequence Listing discloses the amino acid sequences encoded by the described NHP encoding polynucleotides. The NHPs have initiator methionines in DNA sequence contexts consistent with a translation initiation site, and further incorporate a hydrophobic leader sequence characteristic of secreted or membrane associated proteins.

The NHP amino acid sequences of the invention include the amino acid sequence presented in the Sequence Listing as well as analogues and derivatives thereof. Further, corresponding NHP homologues from other species are encompassed by the invention. In fact, any NHP protein encoded by the NHP nucleotide sequences described above are within the scope of the invention, as are any novel polynucleotide sequences encoding all or any novel portion of an amino acid sequence presented in the Sequence Listing. The degenerate nature of the genetic code is well known, and, accordingly, each amino acid presented in the Sequence Listing, is generically representative of the well known nucleic acid "triplet" codon, or in many cases codons, that can encode the amino acid. As such, as contemplated herein, the amino acid sequences presented in the Sequence Listing, when taken together with the genetic code (see, for example, Table 4-1 at page 109 of "Molecular Cell Biology", 1986, J. Darnell *et al.* eds., Scientific American Books, New York, NY, herein incorporated by reference) are generically representative of all the various permutations and combinations of nucleic acid sequences that can encode such amino acid sequences.

The invention also encompasses proteins that are functionally equivalent to the NHPs encoded by the presently described nucleotide sequences as judged by any of a number of criteria, including, but not limited to, the ability to bind and cleave a substrate of a NHP, or the ability to effect an identical or complementary downstream pathway, or a change in cellular metabolism (*e.g.*, proteolytic activity, ion flux, tyrosine

phosphorylation, etc.). Such functionally equivalent NHP proteins include, but are not limited to, additions or substitutions of amino acid residues within the amino acid sequence encoded by the NHP nucleotide sequences described above, but which result in a silent change, thus producing a functionally equivalent gene product. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

A variety of host-expression vector systems can be used to express the NHP nucleotide sequences of the invention. Where, as in the present instance, the NHP peptide or polypeptide is thought to be a soluble or secreted molecule, the peptide or polypeptide can be recovered from the culture media. Alternatively, if the described NHP is membrane associated, as characteristic of some *Notch* ligands, a soluble derivative can be engineered by deleting a transmembrane domain. Such expression systems also encompass engineered host cells that express a NHP, or functional equivalent, *in situ*. Purification or enrichment of a NHP from such expression systems can be accomplished using appropriate detergents and lipid micelles and methods well known to those skilled in the art. However, such engineered host cells themselves may be used in situations where it is important not only to retain the structural and functional characteristics of the NHP, but to assess biological activity, *e.g.*, in drug screening assays.

The expression systems that can be used for purposes of the invention include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing NHP nucleotide sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing NHP nucleotide sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing NHP sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing NHP nucleotide sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the NHP product being expressed. For example, when a large quantity of such a protein is to be produced for the generation of pharmaceutical compositions of or containing NHP, or for raising antibodies to a NHP, vectors that direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, EMBO J. *2*:1791), in which a NHP coding sequence may be ligated individually into the vector in frame with the *lacZ* coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. *13*:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. *264*:5503-5509); and the like. pGEX

vectors (Pharmacia or American Type Culture Collection) can also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The PGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhidrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. A NHP gene coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Successful insertion of NHP gene coding sequence will result in inactivation of the polyhedrin gene and production of non-occluded recombinant virus (*i.e.*, virus lacking the proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect Spodoptera frugiperda cells in which the inserted gene is expressed (*e.g.*, see Smith *et al.*, 1983, J. Virol. 46: 584; Smith, U.S. Patent No. 4,215,051).

In mammalian host cells, a number of viral-based expression systems can be utilized. In cases where an adenovirus is used as an expression vector, the NHP nucleotide sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing a NHP product in infected hosts (*e.g.*, See Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA *81*:3655-3659). Specific initiation signals may also be required for efficient translation

of inserted NHP nucleotide sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire NHP gene or cDNA, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only a portion of a NHP coding sequence is inserted, exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (See Bittner *et al.*, 1987, Methods in Enzymol. *153*:516-544).

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, human cell lines.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the NHP sequences described above can be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the NHP product. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the NHP product.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler, *et al.*, 1977, Cell *11*:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, Proc. Natl. Acad. Sci. USA *48*:2026), and adenine phosphoribosyltransferase (Lowy, *et al.*, 1980, Cell *22*:817) genes can be employed in tk^-, $hgprt^-$ or $aprt^-$ cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler, *et al.*, 1980, Natl. Acad. Sci. USA 77:3567; O'Hare, *et al.*, 1981, Proc. Natl. Acad. Sci. USA *78*:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA *78*:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin, *et al.*,

1981, J. Mol. Biol. *150*:1); and hygro, which confers resistance to hygromycin (Santerre, *et al.*, 1984, Gene *30*:147).

Alternatively, any fusion protein can be readily purified by utilizing an antibody specific for the fusion protein being expressed. For example, a system described by Janknecht *et al.* allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht, *et al.*, 1991, Proc. Natl. Acad. Sci. USA *88*:8972-8976). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the gene's open reading frame is translationally fused to an amino-terminal tag consisting of six histidine residues. Extracts from cells infected with recombinant vaccinia virus are loaded onto Ni^{2+}·nitriloacetic acid-agarose columns and histidine-tagged proteins are selectively eluted with imidazole-containing buffers.

5.3 ANTIBODIES TO NHP PRODUCTS

Antibodies that specifically recognize one or more epitopes of a NHP, or epitopes of conserved variants of a NHP, or peptide fragments of a NHP are also encompassed by the invention. Such antibodies include but are not limited to polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, $F(ab')_2$ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

The antibodies of the invention may be used, for example, in the detection of NHP in a biological sample and may, therefore, be utilized as part of a diagnostic or prognostic technique whereby patients may be tested for abnormal amounts of NHP. Such antibodies may also be utilized in conjunction with, for example, compound screening schemes for the evaluation of the effect of test compounds on expression and/or activity of a NHP gene product. Additionally, such antibodies can be used in conjunction

gene therapy to, for example, evaluate the normal and/or engineered NHP-expressing cells prior to their introduction into the patient. Such antibodies may additionally be used as a method for the inhibition of abnormal NHP activity. Thus, such antibodies may, therefore, be utilized as part of treatment methods.

For the production of antibodies, various host animals may be immunized by injection with the NHP, an NHP peptide (*e.g.*, one corresponding the a functional domain of an NHP), truncated NHP polypeptides (NHP in which one or more domains have been deleted), functional equivalents of the NHP or mutated variant of the NHP. Such host animals may include but are not limited to pigs, rabbits, mice, goats, and rats, to name but a few. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to Freund's adjuvant (complete and incomplete), mineral salts such as aluminum hydroxide or aluminum phosphate, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Alternatively, the immune response could be enhanced by combination and or coupling with molecules such as keyhole limpet hemocyanin, tetanus toxoid, diptheria toxoid, ovalbumin, cholera toxin or fragments thereof. Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of the immunized animals.

Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, can be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, Nature *256*:495-497; and U.S. Patent No. 4,376,110), the human B-

cell hybridoma technique (Kosbor *et al.*, 1983, Immunology Today *4*:72; Cole *et al.*, 1983, Proc. Natl. Acad. Sci. USA *80*:2026-2030), and the EBV-hybridoma technique (Cole *et al.*, 1985, Monoclonal Antibodies And Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated in vitro or in vivo. Production of high titers of mAbs in vivo makes this the presently preferred method of production.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, 1984, Proc. Natl. Acad. Sci., *81*:6851-6855; Neuberger *et al.*, 1984, Nature, *312*:604-608; Takeda *et al.*, 1985, Nature, *314*:452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. Such technologies are described in U.S. Patents Nos. 6,075,181 and 5,877,397 and their respective disclosures which are herein incorporated by reference in their entirety.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778; Bird, 1988, Science *242*:423-426; Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA *85*:5879-5883; and Ward *et al.*, 1989, Nature *334*:544-546) can be adapted to produce single chain antibodies against NHP gene products. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments

include, but are not limited to: the $F(ab')_2$ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed (Huse *et al.*, 1989, Science, *246*:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies to a NHP can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" a given NHP, using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, 1993, FASEB J *7(5)*:437-444; and Nissinoff, 1991, J. Immunol. *147(8)*:2429-2438). For example antibodies which bind to a NHP domain and competitively inhibit the binding of NHP to its cognate receptor can be used to generate anti-idiotypes that "mimic" the NHP and, therefore, bind and activate or neutralize a receptor. Such anti-idiotypic antibodies or Fab fragments of such anti-idiotypes can be used in therapeutic regimens involving a NHP-mediated pathway.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. All cited publications, patents, and patent applications are herein incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in the NHP sequence described in SEQ ID NO:1.

2. An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:4.

4. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:6.

5 An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:8.

6. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:10.

ABSTRACT

Novel human polynucleotide and polypeptide sequences are disclosed that can be used in therapeutic, diagnostic, and pharmacogenomic applications.

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION — **ATTORNEY DOCKET NO.** LEX-0091-USA

As a below named inventor, I hereby declare that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Novel Human Notch Ligand Proteins and Polynucleotides Encoding the Same

the specification of which is attached hereto unless the following box is checked:

( ) was filed on _____ as US Application Serial No. or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
			YES:___ NO:___
			YES:___ NO:___

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE
60/165,959	11/17/1999

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS(patented/pending/abandoned)

POWER OF ATTORNEY:

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) listed below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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caaaatataa cagcagctat ccaattatat gagtccttgg ctaaagaagg atcatgtaaa     540
gcccaaaacg cattaggatt tttgtcttct tatggaatag gaatggaata tgatcaagct     600
aaggcactga tatattacac ctttggaagt gctggaggaa acatgatgtc ccagatgatt     660
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gtggaaaaag tgagactaac ggaaagacct gaaaatctga gttctaacag tgagattttg     840
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gcattacact acttcttaaa ggcagcaaag gccgggagtg caaatgccat ggcatttata    1020
ggaaagatgt atttagaggg gaatgctgcc gtgccgcaaa ataacgctac tgccttcaag    1080
tacttttcca tggcagccag taagggcaat gcaatcggcc ttcatgggct tggtcttctt    1140
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gctgcggaaa aagggtggcc cgacgcacag ttccagttag gcttcatgta ctactctggc    1260
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gagaaattcc tgacagctta ctttgcctat aaggatggtg atatagattc ttctcttgtt    1500
cagtatgcac tgcttgcaga aatggggtat gaagtagctc aaagcaattc agcattcatt    1560
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ggcttaggca tcacaaagga cattcacttg gccagaagat tgtacgacat ggctgctcaa    1860
acgagtccag atgcccacat acctgtgctc tttgccgtca tgaaactgga aactacgcat    1920
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<210> 4
<211> 688
<212> PRT
<213> Homo sapiens

<400> 4

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Met Lys Pro Leu Ser Leu Leu Ile Glu Ile Leu Ile Ile Leu Gly Val
 1               5                  10                  15
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            20                  25                  30
Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu
        35                  40                  45
Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg
    50                  55                  60
Glu Asn Leu Leu Glu Lys Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys
65                  70                  75                  80
Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln
                85                  90                  95
Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys
            100                 105                 110
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Met Gly Ile Lys Val Leu Gln Gln Ser Lys Ser Gln Lys Gln Lys Glu
115 120 125
Glu Ala Tyr Leu Leu Phe Ala Lys Ala Ala Asp Met Gly Asn Leu Lys
130 135 140
Ala Met Glu Lys Met Ala Asp Ala Leu Leu Phe Gly Asn Phe Gly Val
145 150 155 160
Gln Asn Ile Thr Ala Ala Ile Gln Leu Tyr Glu Ser Leu Ala Lys Glu
165 170 175
Gly Ser Cys Lys Ala Gln Asn Ala Leu Gly Phe Leu Ser Ser Tyr Gly
180 185 190
Ile Gly Met Glu Tyr Asp Gln Ala Lys Ala Leu Ile Tyr Tyr Thr Phe
195 200 205
Gly Ser Ala Gly Gly Asn Met Met Ser Gln Met Ile Leu Gly Tyr Arg
210 215 220
Tyr Leu Ser Gly Ile Asn Val Leu Gln Asn Cys Glu Val Ala Leu Ser
225 230 235 240
Tyr Tyr Lys Lys Val Ala Asp Tyr Ile Ala Asp Thr Phe Glu Lys Ser
245 250 255
Glu Gly Val Pro Val Glu Lys Val Arg Leu Thr Glu Arg Pro Glu Asn
260 265 270
Leu Ser Ser Asn Ser Glu Ile Leu Asp Trp Asp Ile Tyr Gln Tyr Tyr
275 280 285
Lys Phe Leu Ala Glu Arg Gly Asp Val Gln Ile Gln Val Ser Leu Gly
290 295 300
Gln Leu His Leu Ile Gly Arg Lys Gly Leu Asp Gln Asp Tyr Tyr Lys
305 310 315 320
Ala Leu His Tyr Phe Leu Lys Ala Ala Lys Ala Gly Ser Ala Asn Ala
325 330 335
Met Ala Phe Ile Gly Lys Met Tyr Leu Glu Gly Asn Ala Ala Val Pro
340 345 350
Gln Asn Asn Ala Thr Ala Phe Lys Tyr Phe Ser Met Ala Ala Ser Lys
355 360 365
Gly Asn Ala Ile Gly Leu His Gly Leu Gly Leu Leu Tyr Phe His Gly
370 375 380
Lys Gly Val Pro Leu Asn Tyr Ala Glu Ala Leu Lys Tyr Phe Gln Lys
385 390 395 400
Ala Ala Glu Lys Gly Trp Pro Asp Ala Gln Phe Gln Leu Gly Phe Met
405 410 415
Tyr Tyr Ser Gly Ser Gly Ile Trp Lys Asp Tyr Lys Leu Ala Phe Lys
420 425 430
Tyr Phe Tyr Leu Ala Ser Gln Ser Gly Gln Pro Leu Ala Ile Tyr Tyr
435 440 445
Leu Ala Lys Met Tyr Ala Thr Gly Thr Gly Val Val Arg Ser Cys Arg
450 455 460
Thr Ala Val Glu Leu Tyr Lys Gly Val Cys Glu Leu Gly His Trp Ala
465 470 475 480
Glu Lys Phe Leu Thr Ala Tyr Phe Ala Tyr Lys Asp Gly Asp Ile Asp
485 490 495
Ser Ser Leu Val Gln Tyr Ala Leu Leu Ala Glu Met Gly Tyr Glu Val
500 505 510
Ala Gln Ser Asn Ser Ala Phe Ile Leu Glu Ser Lys Lys Ala Asn Ile
515 520 525
Leu Glu Lys Glu Lys Met Tyr Pro Met Ala Leu Leu Leu Trp Asn Arg
530 535 540
Ala Ala Ile Gln Gly Asn Ala Phe Ala Arg Val Lys Ile Gly Asp Tyr

545 550 555 560
His Tyr Tyr Gly Tyr Gly Thr Lys Lys Asp Tyr Gln Thr Ala Ala Thr
565 570 575
His Tyr Ser Ile Ala Ala Asn Lys Tyr His Asn Ala Gln Ala Met Phe
580 585 590
Asn Leu Ala Tyr Met Tyr Glu His Gly Leu Gly Ile Thr Lys Asp Ile
595 600 605
His Leu Ala Arg Arg Leu Tyr Asp Met Ala Ala Gln Thr Ser Pro Asp
610 615 620
Ala His Ile Pro Val Leu Phe Ala Val Met Lys Leu Glu Thr Thr His
625 630 635 640
Leu Leu Arg Asp Ile Leu Phe Phe Asn Phe Thr Thr Arg Trp Asn Trp
645 650 655
Leu Lys Leu Asp Asn Thr Ile Gly Pro His Trp Asp Leu Phe Val Ile
660 665 670
Gly Leu Ile Val Pro Gly Leu Ile Leu Leu Leu Arg Asn His His Gly
675 680 685

<210> 5
<211> 1773
<212> DNA
<213> Homo sapiens

<400> 5
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gtgaacgaaa tcaaacaata tttatcacac atattggaac aaagaacatc tagtaatgta 180
atcaataaaa gagaaaatct cctggagaaa aagaagaatc aacgtaaaat aagaataaaa 240
ggaattcaaa ataaagatat cttgaagaga aataagaatc atttacaaaa gcaagcagag 300
aaaaatttta cagatgaagg agaccagcta tttaagatgg gcatcaaggt tctccagcag 360
tctaaaagcc aaaaacaaaa agaagaagcc tacctacttt ttgccaaagc agctgacatg 420
ggaaacttga aagctatgga gaaaatggct gacgctttgc tatttggaaa ttttggcgtg 480
caaaatataa cagcagctat ccaattatat gagtccttgg ctaaagaagg atcatgtaaa 540
gcccaaaacg cattaggatt tttgtcttct tatggaatag gaatggaata tgatcaagct 600
aaggcactga tatattacac ctttggaagt gctggaggaa acatgatgtc ccagatgatt 660
ttggggtaca gatatttgtc gggaatcaat gttctacaga attgtgaagt tgccctaagt 720
tattacaaga aagtggcaga ttatattgct gacacatttg aaaaaagtga aggtgttcca 780
gtggaaaaag tgagactaac ggaaagacct gaaaatctga gttctaacag tgagattttg 840
gattgggaca tataccaata ctataaattt ttggcagaaa gaggagatgt tcagatacaa 900
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gcattacact acttcttaaa ggcagcaaag gccgggagtg caaatgccat ggcatttata 1020
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tactttcca tggcagccag taagggcaat gcaatcggcc ttcatgggct tggtcttctt 1140
tactttcatg gaaaaggagt tcccctgaat tatgccraag cacttaaata ctttcagaaa 1200
gctgcggaaa aagggtggcc cgacgcacag ttccagttag gcttcatgta ctactctggc 1260
tctggaatat ggaaggatta taaacttgcc ttcaaatatt tttacctggc atctcagagt 1320
gggcagcccc tcgccattta ttatctggcc aagatgtatg caacaggaac aggagtagta 1380
agatcatgca gaactgctgt ggagctttat aaaggtgtct gtgaactagg ccactgggct 1440
gagaaattcc tgacagctta ctttgcctat aaggatggtg atatagattc ttctcttgtt 1500
cagtatgcac tgcttgcaga aatggggtat gaagtagctc aaagcaattc agcattcatt 1560
ttggaatcta aaaaggctaa cattcttgaa aaagagaaga tgtatccaat ggcgcttctc 1620
ctatggaatc gagctgccat tcaaggacat tcacttggcc agaagattgt acgacatggc 1680
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tacgcatttg ctccgggata tcctgttttt taa 1773

<210> 6
<211> 590
<212> PRT
<213> Homo sapiens

<400> 6
Met Lys Pro Leu Ser Leu Leu Ile Glu Ile Leu Ile Ile Leu Gly Val
 1   5   10   15
Thr Ile Lys Thr Ile Lys Ala Glu Glu His Asn Lys Arg Gln Lys Glu
            20   25   30
Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu
        35   40   45
Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg
    50   55   60
Glu Asn Leu Leu Glu Lys Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys
65   70   75   80
Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln
                85   90   95
Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys
            100   105   110
Met Gly Ile Lys Val Leu Gln Gln Ser Lys Ser Gln Lys Gln Lys Glu
        115   120   125
Glu Ala Tyr Leu Leu Phe Ala Lys Ala Ala Asp Met Gly Asn Leu Lys
    130   135   140
Ala Met Glu Lys Met Ala Asp Ala Leu Leu Phe Gly Asn Phe Gly Val
145   150   155   160
Gln Asn Ile Thr Ala Ala Ile Gln Leu Tyr Glu Ser Leu Ala Lys Glu
                165   170   175
Gly Ser Cys Lys Ala Gln Asn Ala Leu Gly Phe Leu Ser Ser Tyr Gly
            180   185   190
Ile Gly Met Glu Tyr Asp Gln Ala Lys Ala Leu Ile Tyr Tyr Thr Phe
        195   200   205
Gly Ser Ala Gly Gly Asn Met Met Ser Gln Met Ile Leu Gly Tyr Arg
    210   215   220
Tyr Leu Ser Gly Ile Asn Val Leu Gln Asn Cys Glu Val Ala Leu Ser
225   230   235   240
Tyr Tyr Lys Lys Val Ala Asp Tyr Ile Ala Asp Thr Phe Glu Lys Ser
                245   250   255
Glu Gly Val Pro Val Glu Lys Val Arg Leu Thr Glu Arg Pro Glu Asn
            260   265   270
Leu Ser Ser Asn Ser Glu Ile Leu Asp Trp Asp Ile Tyr Gln Tyr Tyr
        275   280   285
Lys Phe Leu Ala Glu Arg Gly Asp Val Gln Ile Gln Val Ser Leu Gly
    290   295   300
Gln Leu His Leu Ile Gly Arg Lys Gly Leu Asp Gln Asp Tyr Tyr Lys
305   310   315   320
Ala Leu His Tyr Phe Leu Lys Ala Ala Lys Ala Gly Ser Ala Asn Ala
                325   330   335
Met Ala Phe Ile Gly Lys Met Tyr Leu Glu Gly Asn Ala Ala Val Pro
            340   345   350
Gln Asn Asn Ala Thr Ala Phe Lys Tyr Phe Ser Met Ala Ala Ser Lys
        355   360   365
Gly Asn Ala Ile Gly Leu His Gly Leu Gly Leu Leu Tyr Phe His Gly
    370   375   380
Lys Gly Val Pro Leu Asn Tyr Ala Glu Ala Leu Lys Tyr Phe Gln Lys

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385                 390                 395                 400
Ala Ala Glu Lys Gly Trp Pro Asp Ala Gln Phe Gln Leu Gly Phe Met
                405                 410                 415
Tyr Tyr Ser Gly Ser Gly Ile Trp Lys Asp Tyr Lys Leu Ala Phe Lys
            420                 425                 430
Tyr Phe Tyr Leu Ala Ser Gln Ser Gly Gln Pro Leu Ala Ile Tyr Tyr
        435                 440                 445
Leu Ala Lys Met Tyr Ala Thr Gly Thr Gly Val Val Arg Ser Cys Arg
    450                 455                 460
Thr Ala Val Glu Leu Tyr Lys Gly Val Cys Glu Leu Gly His Trp Ala
465                 470                 475                 480
Glu Lys Phe Leu Thr Ala Tyr Phe Ala Tyr Lys Asp Gly Asp Ile Asp
                485                 490                 495
Ser Ser Leu Val Gln Tyr Ala Leu Leu Ala Glu Met Gly Tyr Glu Val
            500                 505                 510
Ala Gln Ser Asn Ser Ala Phe Ile Leu Glu Ser Lys Lys Ala Asn Ile
        515                 520                 525
Leu Glu Lys Glu Lys Met Tyr Pro Met Ala Leu Leu Leu Trp Asn Arg
    530                 535                 540
Ala Ala Ile Gln Gly His Ser Leu Gly Gln Lys Ile Val Arg His Gly
545                 550                 555                 560
Cys Ser Asn Glu Ser Arg Cys Pro His Thr Cys Ala Leu Cys Arg His
                565                 570                 575
Glu Thr Gly Asn Tyr Ala Phe Ala Pro Gly Tyr Pro Val Phe
            580                 585                 590
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<210> 7
<211> 1257
<212> DNA
<213> Homo sapiens

<400> 7

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gtgaacgaaa tcaaacaata tttatcacac atattggaac aaagaacatc tagtaatgta     180
atcaataaaa gagaaaatct cctggagaaa aagaagaatc aacgtaaaat aagaataaaa     240
ggaattcaaa ataaagatat cttgaagaga aataagaatc atttacaaaa gcaagcagag     300
aaaaatttta cagatgaagg agaccagcta tttaagatgg gcatcaaggt tctccagcag     360
tctaaaagcc aaaaacaaaa agaagaagcc tacctacttt ttgccaaagc agctgacatg     420
ggaaacttga aagctatgga gaaaatggct gacgctttgc tatttggaaa ttttggcgtg     480
caaaatataa cagcagctat ccaattatat gagtccttgg ctaaagaagg atcatgtaaa     540
gcccaaaacg cattaggatt tttgtcttct tatggaatag gaatggaata tgatcaagct     600
aaggcactga tatattacac ctttggaagt gctggaggaa acatgatgtc ccagatgatt     660
ttggggtaca gatatttgtc gggaatcaat gttctacaga attgtgaagt tgccctaagt     720
tattacaaga aagtggcaga ttatattgct gacacatttg aaaaaagtga aggtgttcca     780
gtggaaaaag tgagactaac ggaaagacct gaaaatctga gttctaacag tgagattttg     840
gattgggaca tataccaata ctataaattt ttggcagaaa gaggagatgt tcagatacaa     900
gtctctcttg gacaattaca tctaattggc aggaaaggtc tagatcagga ttactacaaa     960
gcattacact acttcttaaa ggcagcaaag gccgggagtg caaatgccat ggcatttata    1020
ggaaagatgt atttagaggg gaatgctgcc gtgccgcaaa ataacgctac tgccttcaag    1080
tacttttcca tggcagccag taagggcaat gcaatcggcc ttcatgggct tggtcttctt    1140
tactttcatg gaaaaggagt tcccctgaat tatgccraag cacttaaata ctttcagaaa    1200
gctgcggaaa aagggtggcc cgacgcacag ttccagttag gcttcatgta ctactaa       1257
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<210> 8

<211> 418
<212> PRT
<213> Homo sapiens

<400> 8
Met Lys Pro Leu Ser Leu Leu Ile Glu Ile Leu Ile Ile Leu Gly Val
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Thr Ile Lys Thr Ile Lys Ala Glu Glu His Asn Lys Arg Gln Lys Glu
            20   25   30
Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu
        35   40   45
Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg
    50   55   60
Glu Asn Leu Leu Glu Lys Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys
65   70   75   80
Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln
                85   90   95
Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys
            100   105   110
Met Gly Ile Lys Val Leu Gln Gln Ser Lys Ser Gln Lys Gln Lys Glu
        115   120   125
Glu Ala Tyr Leu Leu Phe Ala Lys Ala Ala Asp Met Gly Asn Leu Lys
    130   135   140
Ala Met Glu Lys Met Ala Asp Ala Leu Leu Phe Gly Asn Phe Gly Val
145   150   155   160
Gln Asn Ile Thr Ala Ala Ile Gln Leu Tyr Glu Ser Leu Ala Lys Glu
                165   170   175
Gly Ser Cys Lys Ala Gln Asn Ala Leu Gly Phe Leu Ser Ser Tyr Gly
            180   185   190
Ile Gly Met Glu Tyr Asp Gln Ala Lys Ala Leu Ile Tyr Tyr Thr Phe
        195   200   205
Gly Ser Ala Gly Gly Asn Met Met Ser Gln Met Ile Leu Gly Tyr Arg
    210   215   220
Tyr Leu Ser Gly Ile Asn Val Leu Gln Asn Cys Glu Val Ala Leu Ser
225   230   235   240
Tyr Tyr Lys Lys Val Ala Asp Tyr Ile Ala Asp Thr Phe Glu Lys Ser
                245   250   255
Glu Gly Val Pro Val Glu Lys Val Arg Leu Thr Glu Arg Pro Glu Asn
            260   265   270
Leu Ser Ser Asn Ser Glu Ile Leu Asp Trp Asp Ile Tyr Gln Tyr Tyr
        275   280   285
Lys Phe Leu Ala Glu Arg Gly Asp Val Gln Ile Gln Val Ser Leu Gly
    290   295   300
Gln Leu His Leu Ile Gly Arg Lys Gly Leu Asp Gln Asp Tyr Tyr Lys
305   310   315   320
Ala Leu His Tyr Phe Leu Lys Ala Ala Lys Ala Gly Ser Ala Asn Ala
                325   330   335
Met Ala Phe Ile Gly Lys Met Tyr Leu Glu Gly Asn Ala Ala Val Pro
            340   345   350
Gln Asn Asn Ala Thr Ala Phe Lys Tyr Phe Ser Met Ala Ala Ser Lys
        355   360   365
Gly Asn Ala Ile Gly Leu His Gly Leu Gly Leu Leu Tyr Phe His Gly
    370   375   380
Lys Gly Val Pro Leu Asn Tyr Ala Glu Ala Leu Lys Tyr Phe Gln Lys
385   390   395   400

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Ala Ala Glu Lys Gly Trp Pro Asp Ala Gln Phe Gln Leu Gly Phe Met
                405                 410                 415
Tyr Tyr
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<210> 9
<211> 1500
<212> DNA
<213> Homo sapiens

<400> 9

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gtgaacgaaa tcaaacaata tttatcacac atattggaac aaagaacatc tagtaatgta     180
atcaataaaa gagaaaatct cctggagaaa aagaagaatc aacgtaaaat aagaataaaa     240
ggaattcaaa ataaagatat cttgaagaga aataagaatc atttacaaaa gcaagcagag     300
aaaaatttta cagatgaagg agaccagcta tttaagatgg gcatcaaggt tctccagcag     360
tctaaaagcc aaaaacaaaa agaagaagcc tacctacttt ttgccaaagc agctgacatg     420
ggaaacttga aagctatgga gaaaatggct gacgctttgc tatttggaaa ttttggcgtg     480
caaaatataa cagcagctat ccaattatat gagtccttgg ctaaagaagg atcatgtaaa     540
gcccaaaacg cattaggatt tttgtcttct tatggaatag gaatggaata tgatcaagct     600
aaggcactga tatattacac ctttggaagt gctggaggaa acatgatgtc ccagatgatt     660
ttggggtaca gatatttgtc gggaatcaat gttctacaga attgtgaagt tgccctaagt     720
tattacaaga aagtggcaga ttatattgct gacacatttg aaaaaagtga aggtgttcca     780
gtggaaaaag tgagactaac ggaaagacct gaaaatctga gttctaacag tgagattttg     840
gattgggaca tataccaata ctataaattt ttggcagaaa gaggagatgt tcagatacaa     900
gtctctcttg gacaattaca tctaattggc aggaaaggtc tagatcagga ttactacaaa     960
gcattacact acttcttaaa ggcagcaaag gccgggagtg caaatgccat ggcatttata    1020
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tacttttcca tggcagccag taagggcaat gcaatcggcc ttcatgggct tggtcttctt    1140
tactttcatg gaaaaggagt tcccctgaat tatgccraag cacttaaata ctttcagaaa    1200
gctgcggaaa aagggtggcc cgacgcacag ttccagttag gcttcatgta ctactctggc    1260
tctggaatat ggaaggatta taaacttgcc ttcaaatatt tttacctggc atctcagagt    1320
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agatcatgca gaactgctgt ggagaaaagg ctaacattct tgaaaaagag aagatgtatc    1440
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<210> 10
<211> 499
<212> PRT
<213> Homo sapiens

<400> 10

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Met Lys Pro Leu Ser Leu Leu Ile Glu Ile Leu Ile Ile Leu Gly Val
 1               5                  10                  15
Thr Ile Lys Thr Ile Lys Ala Glu Glu His Asn Lys Arg Gln Lys Glu
            20                  25                  30
Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu
        35                  40                  45
Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg
    50                  55                  60
Glu Asn Leu Leu Glu Lys Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys
65                  70                  75                  80
Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln
                85                  90                  95
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Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys
100 105 110
Met Gly Ile Lys Val Leu Gln Gln Ser Lys Ser Gln Lys Gln Lys Glu
115 120 125
Glu Ala Tyr Leu Leu Phe Ala Lys Ala Ala Asp Met Gly Asn Leu Lys
130 135 140
Ala Met Glu Lys Met Ala Asp Ala Leu Leu Phe Gly Asn Phe Gly Val
145 150 155 160
Gln Asn Ile Thr Ala Ala Ile Gln Leu Tyr Glu Ser Leu Ala Lys Glu
165 170 175
Gly Ser Cys Lys Ala Gln Asn Ala Leu Gly Phe Leu Ser Ser Tyr Gly
180 185 190
Ile Gly Met Glu Tyr Asp Gln Ala Lys Ala Leu Ile Tyr Tyr Thr Phe
195 200 205
Gly Ser Ala Gly Gly Asn Met Met Ser Gln Met Ile Leu Gly Tyr Arg
210 215 220
Tyr Leu Ser Gly Ile Asn Val Leu Gln Asn Cys Glu Val Ala Leu Ser
225 230 235 240
Tyr Tyr Lys Lys Val Ala Asp Tyr Ile Ala Asp Thr Phe Glu Lys Ser
245 250 255
Glu Gly Val Pro Val Glu Lys Val Arg Leu Thr Glu Arg Pro Glu Asn
260 265 270
Leu Ser Ser Asn Ser Glu Ile Leu Asp Trp Asp Ile Tyr Gln Tyr Tyr
275 280 285
Lys Phe Leu Ala Glu Arg Gly Asp Val Gln Ile Gln Val Ser Leu Gly
290 295 300
Gln Leu His Leu Ile Gly Arg Lys Gly Leu Asp Gln Asp Tyr Tyr Lys
305 310 315 320
Ala Leu His Tyr Phe Leu Lys Ala Ala Lys Ala Gly Ser Ala Asn Ala
325 330 335
Met Ala Phe Ile Gly Lys Met Tyr Leu Glu Gly Asn Ala Ala Val Pro
340 345 350
Gln Asn Asn Ala Thr Ala Phe Lys Tyr Phe Ser Met Ala Ala Ser Lys
355 360 365
Gly Asn Ala Ile Gly Leu His Gly Leu Gly Leu Leu Tyr Phe His Gly
370 375 380
Lys Gly Val Pro Leu Asn Tyr Ala Glu Ala Leu Lys Tyr Phe Gln Lys
385 390 395 400
Ala Ala Glu Lys Gly Trp Pro Asp Ala Gln Phe Gln Leu Gly Phe Met
405 410 415
Tyr Tyr Ser Gly Ser Gly Ile Trp Lys Asp Tyr Lys Leu Ala Phe Lys
420 425 430
Tyr Phe Tyr Leu Ala Ser Gln Ser Gly Gln Pro Leu Ala Ile Tyr Tyr
435 440 445
Leu Ala Lys Met Tyr Ala Thr Gly Thr Gly Val Val Arg Ser Cys Arg
450 455 460
Thr Ala Val Glu Lys Arg Leu Thr Phe Leu Lys Lys Arg Arg Cys Ile
465 470 475 480
Gln Trp Arg Phe Ser Tyr Gly Ile Glu Leu Pro Phe Lys Ala Met His
485 490 495
Leu Leu Glu

<210> 11
<211> 1731

<212> DNA
<213> Homo sapiens

<400> 11
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gtgaacgaaa tcaaacaata tttatcacac atattggaac aaagaacatc tagtaatgta 180
atcaataaaa gagaaaatct cctggagaaa aagaagaatc aacgtaaaat aagaataaaa 240
ggaattcaaa ataaagatat cttgaagaga aataagaatc atttacaaaa gcaagcagag 300
aaaaatttta cagatgaagg agaccagcta tttaagatgg gcatcaaggt tctccagcag 360
tctaaaagcc aaaaacaaaa agaagaagcc tacctacttt ttgccaaagc agctgacatg 420
ggaaacttga aagctatgga gaaaatggct gacgctttgc tatttggaaa ttttggcgtg 480
caaaatataa cagcagctat ccaattatat gagtccttgg ctaaagaagg atcatgtaaa 540
gcccaaaacg cattaggatt tttgtcttct tatggaatag gaatggaata tgatcaagct 600
aaggcactga tatattacac ctttggaagt gctggaggaa acatgatgtc ccagatgatt 660
ttggggtaca gatatttgtc gggaatcaat gttctacaga attgtgaagt tgccctaagt 720
tattacaaga aagtggcaga ttatattgct gacacatttg aaaaaagtga aggtgttcca 780
gtggaaaaag tgagactaac ggaaagacct gaaaatctga gttctaacag tgagattttg 840
gattgggaca tataccaata ctataaattt ttggcagaaa gaggagatgt tcagatacaa 900
gtctctcttg gacaattaca tctaattggc aggaaaggtc tagatcagga ttactacaaa 960
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tacttttcca tggcagccag taagggcaat gcaatcggcc ttcatgggct tggtcttctt 1140
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gctgcggaaa aagggtggcc cgacgcacag ttccagttag gcttcatgta ctactctggc 1260
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agatcatgca gaactgctgt ggagaaaagg ctaacattct tgaaaaagag aagatgtatc 1440
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ttgtacgaca tggctgctca aacgagtcca gatgcccaca tacctgtgct ctttgccgtc 1560
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agatggaact ggctgaaact ggacaacacc attggaccac actgggactt atttgtgatt 1680
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<210> 12
<211> 576
<212> PRT
<213> Homo sapiens

<400> 12
Met Lys Pro Leu Ser Leu Leu Ile Glu Ile Leu Ile Ile Leu Gly Val
 1   5   10   15
Thr Ile Lys Thr Ile Lys Ala Glu Glu His Asn Lys Arg Gln Lys Glu
            20   25   30
Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu
        35   40   45
Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg
    50   55   60
Glu Asn Leu Leu Glu Lys Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys
65   70   75   80
Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln
                85   90   95
Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys
            100   105   110
Met Gly Ile Lys Val Leu Gln Gln Ser Lys Ser Gln Lys Gln Lys Glu

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        115                 120                 125
Glu Ala Tyr Leu Leu Phe Ala Lys Ala Ala Asp Met Gly Asn Leu Lys
    130                 135                 140
Ala Met Glu Lys Met Ala Asp Ala Leu Leu Phe Gly Asn Phe Gly Val
145                 150                 155                 160
Gln Asn Ile Thr Ala Ala Ile Gln Leu Tyr Glu Ser Leu Ala Lys Glu
                165                 170                 175
Gly Ser Cys Lys Ala Gln Asn Ala Leu Gly Phe Leu Ser Ser Tyr Gly
            180                 185                 190
Ile Gly Met Glu Tyr Asp Gln Ala Lys Ala Leu Ile Tyr Tyr Thr Phe
        195                 200                 205
Gly Ser Ala Gly Gly Asn Met Met Ser Gln Met Ile Leu Gly Tyr Arg
    210                 215                 220
Tyr Leu Ser Gly Ile Asn Val Leu Gln Asn Cys Glu Val Ala Leu Ser
225                 230                 235                 240
Tyr Tyr Lys Lys Val Ala Asp Tyr Ile Ala Asp Thr Phe Glu Lys Ser
                245                 250                 255
Glu Gly Val Pro Val Glu Lys Val Arg Leu Thr Glu Arg Pro Glu Asn
            260                 265                 270
Leu Ser Ser Asn Ser Glu Ile Leu Asp Trp Asp Ile Tyr Gln Tyr Tyr
        275                 280                 285
Lys Phe Leu Ala Glu Arg Gly Asp Val Gln Ile Gln Val Ser Leu Gly
    290                 295                 300
Gln Leu His Leu Ile Gly Arg Lys Gly Leu Asp Gln Asp Tyr Tyr Lys
305                 310                 315                 320
Ala Leu His Tyr Phe Leu Lys Ala Ala Lys Ala Gly Ser Ala Asn Ala
                325                 330                 335
Met Ala Phe Ile Gly Lys Met Tyr Leu Glu Gly Asn Ala Ala Val Pro
            340                 345                 350
Gln Asn Asn Ala Thr Ala Phe Lys Tyr Phe Ser Met Ala Ala Ser Lys
        355                 360                 365
Gly Asn Ala Ile Gly Leu His Gly Leu Gly Leu Leu Tyr Phe His Gly
    370                 375                 380
Lys Gly Val Pro Leu Asn Tyr Ala Glu Ala Leu Lys Tyr Phe Gln Lys
385                 390                 395                 400
Ala Ala Glu Lys Gly Trp Pro Asp Ala Gln Phe Gln Leu Gly Phe Met
                405                 410                 415
Tyr Tyr Ser Gly Ser Gly Ile Trp Lys Asp Tyr Lys Leu Ala Phe Lys
            420                 425                 430
Tyr Phe Tyr Leu Ala Ser Gln Ser Gly Gln Pro Leu Ala Ile Tyr Tyr
        435                 440                 445
Leu Ala Lys Met Tyr Ala Thr Gly Thr Gly Val Val Arg Ser Cys Arg
    450                 455                 460
Thr Ala Val Glu Lys Arg Leu Thr Phe Leu Lys Lys Arg Arg Cys Ile
465                 470                 475                 480
Gln Trp Arg Phe Ser Tyr Gly Ile Glu Leu Pro Phe Lys Asp Ile His
                485                 490                 495
Leu Ala Arg Arg Leu Tyr Asp Met Ala Ala Gln Thr Ser Pro Asp Ala
            500                 505                 510
His Ile Pro Val Leu Phe Ala Val Met Lys Leu Glu Thr Thr His Leu
        515                 520                 525
Leu Arg Asp Ile Leu Phe Phe Asn Gln Phe Thr Thr Arg Trp Asn Trp
    530                 535                 540
Leu Lys Leu Asp Asn Thr Ile Gly Pro His Trp Asp Leu Phe Val Ile
545                 550                 555                 560
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Gly Leu Ile Val Pro Gly Leu Ile Leu Leu Arg Asn His His Gly
                565                 570                 575

<210> 13
<211> 1728
<212> DNA
<213> Homo sapiens

<400> 13
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gtgaacgaaa tcaaacaata tttatcacac atattggaac aaagaacatc tagtaatgta     180
atcaataaaa gagaaaatct cctggagaaa aagaagaatc aacgtaaaat aagaataaaa     240
ggaattcaaa ataaagatat cttgaagaga aataagaatc atttacaaaa gcaagcagag     300
aaaaatttta cagatgaagg agaccagcta tttaagatgg gcatcaaggt tctccagcag     360
tctaaaagcc aaaaacaaaa agaagaagcc tacctacttt ttgccaaagc agctgacatg     420
ggaaacttga aagctatgga gaaaatggct gacgctttgc tatttggaaa ttttggcgtg     480
caaaatataa cagcagctat ccaattatat gagtccttgg ctaaagaagg atcatgtaaa     540
gcccaaaacg cattaggatt tttgtcttct tatggaatag gaatggaata tgatcaagct     600
aaggcactga tatattacac ctttggaagt gctggaggaa acatgatgtc ccagatgatt     660
ttggggtaca gatatttgtc gggaatcaat gttctacaga attgtgaagt tgccctaagt     720
tattacaaga aagtggcaga ttatattgct gacacatttg aaaaaagtga aggtgttcca     780
gtggaaaaag tgagactaac ggaaagacct gaaaatctga gttctaacag tgagattttg     840
gattgggaca tataccaata ctataaattt ttggcagaaa gaggagatgt tcagatacaa     900
gtctctcttg gacaattaca tctaattggc aggaaaggtc tagatcagga ttactacaaa     960
gcattacact acttcttaaa ggcagcaaag gccgggagtg caaatgccat ggcatttata    1020
ggaaagatgt atttagaggg gaatgctgcc gtgccgcaaa ataacgctac tgccttcaag    1080
tacttttcca tggcagccag taagggcaat gcaatcggcc ttcatgggct tggtcttctt    1140
tactttcatg gaaaaggagt tcccctgaat tatgccraag cacttaaata ctttcagaaa    1200
gctgcggaaa aagggtggcc cgacgcacag ttccagttag gcttcatgta ctactctggc    1260
tctggaatat ggaaggatta taaacttgcc ttcaaatatt tttacctggc atctcagagt    1320
gggcagcccc tcgccattta ttatctggcc aagatgtatg caacaggaac aggagtagta    1380
agatcatgca gaactgctgt ggagaaaagg ctaacattct tgaaaaagag aagatgtatc    1440
caatggcgct tctcctatgg aatcgagctg ccattcaagg acattcactt ggccagaaga    1500
ttgtacgaca tggctgctca aacgagtcca gatgcccaca tacctgtgct ctttgccgtc    1560
atgaaactgg aaactacgca tttgctccgg gatatcctgt tttttaattt cacaacgaga    1620
tggaactggc tgaaactgga caacaccatt ggaccacact gggacttatt tgtgattggc    1680
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<210> 14
<211> 575
<212> PRT
<213> Homo sapiens

<400> 14
Met Lys Pro Leu Ser Leu Leu Ile Glu Ile Leu Ile Ile Leu Gly Val
 1               5                  10                  15
Thr Ile Lys Thr Ile Lys Ala Glu Glu His Asn Lys Arg Gln Lys Glu
            20                  25                  30
Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu
        35                  40                  45
Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg
    50                  55                  60
Glu Asn Leu Leu Glu Lys Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys
65                  70                  75                  80
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Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln
                85                  90                  95
Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys
            100                 105                 110
Met Gly Ile Lys Val Leu Gln Gln Ser Lys Ser Gln Lys Gln Lys Glu
        115                 120                 125
Glu Ala Tyr Leu Leu Phe Ala Lys Ala Ala Asp Met Gly Asn Leu Lys
    130                 135                 140
Ala Met Glu Lys Met Ala Asp Ala Leu Leu Phe Gly Asn Phe Gly Val
145                 150                 155                 160
Gln Asn Ile Thr Ala Ala Ile Gln Leu Tyr Glu Ser Leu Ala Lys Glu
                165                 170                 175
Gly Ser Cys Lys Ala Gln Asn Ala Leu Gly Phe Leu Ser Ser Tyr Gly
            180                 185                 190
Ile Gly Met Glu Tyr Asp Gln Ala Lys Ala Leu Ile Tyr Tyr Thr Phe
        195                 200                 205
Gly Ser Ala Gly Gly Asn Met Met Ser Gln Met Ile Leu Gly Tyr Arg
    210                 215                 220
Tyr Leu Ser Gly Ile Asn Val Leu Gln Asn Cys Glu Val Ala Leu Ser
225                 230                 235                 240
Tyr Tyr Lys Lys Val Ala Asp Tyr Ile Ala Asp Thr Phe Glu Lys Ser
                245                 250                 255
Glu Gly Val Pro Val Glu Lys Val Arg Leu Thr Glu Arg Pro Glu Asn
            260                 265                 270
Leu Ser Ser Asn Ser Glu Ile Leu Asp Trp Asp Ile Tyr Gln Tyr Tyr
        275                 280                 285
Lys Phe Leu Ala Glu Arg Gly Asp Val Gln Ile Gln Val Ser Leu Gly
    290                 295                 300
Gln Leu His Leu Ile Gly Arg Lys Gly Leu Asp Gln Asp Tyr Tyr Lys
305                 310                 315                 320
Ala Leu His Tyr Phe Leu Lys Ala Ala Lys Ala Gly Ser Ala Asn Ala
                325                 330                 335
Met Ala Phe Ile Gly Lys Met Tyr Leu Glu Gly Asn Ala Ala Val Pro
            340                 345                 350
Gln Asn Asn Ala Thr Ala Phe Lys Tyr Phe Ser Met Ala Ala Ser Lys
        355                 360                 365
Gly Asn Ala Ile Gly Leu His Gly Leu Gly Leu Leu Tyr Phe His Gly
    370                 375                 380
Lys Gly Val Pro Leu Asn Tyr Ala Glu Ala Leu Lys Tyr Phe Gln Lys
385                 390                 395                 400
Ala Ala Glu Lys Gly Trp Pro Asp Ala Gln Phe Gln Leu Gly Phe Met
                405                 410                 415
Tyr Tyr Ser Gly Ser Gly Ile Trp Lys Asp Tyr Lys Leu Ala Phe Lys
            420                 425                 430
Tyr Phe Tyr Leu Ala Ser Gln Ser Gly Gln Pro Leu Ala Ile Tyr Tyr
        435                 440                 445
Leu Ala Lys Met Tyr Ala Thr Gly Thr Gly Val Val Arg Ser Cys Arg
    450                 455                 460
Thr Ala Val Glu Lys Arg Leu Thr Phe Leu Lys Lys Arg Arg Cys Ile
465                 470                 475                 480
Gln Trp Arg Phe Ser Tyr Gly Ile Glu Leu Pro Phe Lys Asp Ile His
                485                 490                 495
Leu Ala Arg Arg Leu Tyr Asp Met Ala Ala Gln Thr Ser Pro Asp Ala
            500                 505                 510
His Ile Pro Val Leu Phe Ala Val Met Lys Leu Glu Thr Thr His Leu
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        515                 520                 525
Leu Arg Asp Ile Leu Phe Phe Asn Phe Thr Thr Arg Trp Asn Trp Leu
    530                 535                 540
Lys Leu Asp Asn Thr Ile Gly Pro His Trp Asp Leu Phe Val Ile Gly
545                 550                 555                 560
Leu Ile Val Pro Gly Leu Ile Leu Leu Leu Arg Asn His His Gly
                565                 570                 575
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